Period frequency of iliofemoral venous occlusive disease by Doppler ultrasound and corresponding treatment in a tertiary care facility

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Background: **Patients with iliofemoral deep venous thrombosis (DVT) are at highest risk for the postthrombotic morbidity including all aspects of the postthrombotic syndrome. Invasive therapies such as catheter-directed thrombolysis (CDT) and/or mechanical thrombectomy with or without angioplasty and stenting and in some cases open operative thrombectomy improves venous patency, venous valve function, and quality of life in patients with acute iliofemoral DVT. What is the current frequency of acute iliofemoral DVT and how aggressively is it being treated? We hypothesize that the 10-year period frequency of iliofemoral DVT among acute DVT cases is greater than previously reported. Further, we hypothesize that thrombus removal to treat acute iliofemoral DVT is little utilized in current practice.**

Methods: **Indiana University (IU) vascular laboratory records from January 1, 1998 to December 31, 2008 were searched by CPT code for venous Doppler ultrasound study (n = 7240). A random sample based on the IU medical record number of lower extremity Doppler studies was then selected (n = 1020) for retrospective chart review. Corresponding clinical information was gathered from the patients' electronic medical record.**

Results: **Acute DVT occurred in 6.8%, and chronic DVT in 8.8% of patients studied (25.7% inpatient, 61.7% female; median age, 56.0 years [range, 4-91 years, 1.1% less than 16 years]). History of previous DVT (33.3%) and cancer (30.4%) were the most common risk factors in patients with acute DVT. Iliofemoral DVT defined as having an iliac *or* common femoral vein component was identified in 49.3% of acute DVT and in 36.0% of chronic DVT. CDT was utilized in 14.3% and mechanical thrombectomy in 4.8% of acute iliofemoral DVT, and was never used with distal DVT. Warfarin anticoagulation + unfractionated heparin or low-molecular-weight heparin overlap was the most common treatment for acute iliofemoral DVT (100.0%). In 2008, the referral base of our laboratory increased significantly. Acute DVT occurred significantly less often during the 1-year period 2008 (5.3%) than the 10-year period 1998-2007 (7.6%), but iliofemoral + common femoral DVT as a component of acute DVT did not differ significantly.**

Conclusions: **Iliofemoral DVT may be more frequent than previously reported and represents a significant portion of acute DVT. Current recommendations of acute thrombus removal for the treatment of iliofemoral DVT is underutilized suggesting that perhaps greater education of clinicians and patients regarding invasive therapy for iliofemoral DVT is required. (J Vasc Surg 2010;52:1272-7.)**

Iliofemoral deep venous thrombosis (DVT) carries significant physical, social, and economic consequences. Patients with iliofemoral DVT are at highest risk for postthrombotic morbidity including the postthrombotic syndrome (PTS).[1-3] In addition, recent studies suggest that patients with high proximal (iliac *or* proximal femoral vein) DVT have significantly worse PTS severity than those with distal or popliteal vein DVT.[4-7]

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This work was supported by internal funding of the Section of Vascular Surgery, Department of Surgery, Indiana University.

Competition of interest: none.

Presented at the Twenty-second Annual Meeting of the American Venous Forum, February 10-13, 2010, Amelia Island, Fla.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a competition of interest.

0741-5214/$36.00

doi:10.1016/j.jvs.2010.05.108

Until recently, recommendations and standard of care for this subset of venous occlusive disease was largely the same as for DVT occurring more distally: systemic anticoagulation alone. However, as surgical methodology has advanced and catheterization technology has improved, numerous studies have surfaced documenting that thrombus removal in addition to adequate anticoagulation improves morbidity after iliofemoral DVT.[8] The most recent Chest guidelines reflect these conclusions.[9] The guidelines now recommend catheter-directed thrombolysis (CDT) for extensive acute proximal (iliofemoral) DVT of less than 14 days since onset in patients with good functional status and life expectancy greater than 1 year.[10] Recommendations also include pharmacomechanical thrombolysis in preference to CDT alone to shorten treatment,[11-12] and balloon angioplasty and stenting to correct underlying venous lesions after CDT,[13] followed by anticoagulation therapy.

Despite an increasing focus on iliofemoral DVT, the true rate of iliofemoral disease is not known and the definition not uniform. What then is the current frequency of acute iliofemoral DVT and how aggressively is it being treated? The primary purpose of this study is to perform a

retrospective chart review of patients screened for DVT at the Clarian/IU Vascular Diagnostic Laboratory. The goal is to identify the frequency of iliofemoral DVT in the screened population. The frequency of treatments pursued (systemic thrombolysis, intravenous CDT, open thrombectomy, pharmacomechanical thrombectomy, anticoagulation alone) will also be identified.

METHODS

Patients. The Indiana University School of Medicine serves the Clarian Hospital System (Methodist Hospital, University Hospital, Riley Hospital for Children). One of the Clarian system hospitals is a regional children's hospital, whereas the other two are tertiary-quaternary care facilities. Corresponding clinical information was gathered from the patients' electronic medical record in Cerner PowerChart and the office outpatient clinic chart. Such information included patient history, presenting signs and symptoms, laboratory results, treatment, and outcome if available. None of the 18 HIPAA identifiers were acquired. The protocol and conduct of this retrospective study were reviewed and approved by the Indiana University Institutional Review Board.

Selection protocol. The IU School of Medicine Vascular Surgery maintains a database (Vascubase; Consensus Medical Systems, Inc, Seattle, Wash) of all Doppler studies performed by our staff at the Clarian Hospital System. Indiana University Vascular laboratory records from January 1, 1998 to December 31, 2008 were searched by CPT code (93970, 93971, 93971RT, 93971LT) for venous Doppler ultrasound studies (n = 7240). No practice at the IU/Clarian Hospital system routinely performs venous Doppler studies in asymptomatic patients. The Department of Radiology also performed venous Doppler studies until 2008, but these records were not included in this study. No specific referral pattern for venous studies between the IU Vascular Lab and the Department of Radiology was enforced during this time period.

The Clarian Hospital System assigns all patients to a medical record number based upon date of entrance (first point of care) into the hospital system. The medical record number is assigned to patients without bias toward age, gender, or comorbidity. Studies were numerically ordered by medical record number and one out of every seven studies was consecutively chosen. Thus, a random sample based on the IU medical record number of lower extremity Doppler studies was then selected (n = 1020) for retrospective chart review.

Ultrasound. In all patients, venous duplex ultrasonography was obtained. Our protocol includes routine imaging from distal calf veins to the external iliac vein. More proximal imaging (eg, common iliac) is obtained depending on the presence of an abnormal respiratory or distal augmentation waveform in the common femoral or external iliac vein and/or the presence of DVT in these same areas but is hindered in some cases by body habitus and other patient variables. The criteria for acute DVT included a new noncompressible vein segment, low level echogenicity, acoustic homogeneity, smooth thrombus surface characteristics, venous dilation, and an increase in vein diameter of a known previous thrombus. The criteria for chronic DVT included a small noncompressible vein, high-level echogenicity, acoustic heterogeneity, irregular thrombus surface characteristics, and presence of collateral venous channels and recanalized segments. Acute thrombosis on top of chronic changes was categorized as acute DVT.

Study classification of lower extremity DVT location. DVT was classified into categories according to the most proximal vein segment involved. The location categories were distal (calf vein), popliteal, femoral (superficial or deep), common femoral, or iliac. Iliofemoral DVT was defined as DVT involving iliac and/or common femoral vein as the most proximal segment.

Treatment. Treatment categories included: aspirin, 81 mg or 325 mg daily alone; clopidogrel, 75 mg daily; low-dose prophylactic unfractionated heparin or low-molecular-weight heparin (usually enoxaparin); full-dose intravenous unfractionated heparin, with a target-activated partial thromboplastin time (aPTT) of 60 to 85 seconds or two to three times the control aPTT value or enoxaparin 1 mg per kg twice-daily by subcutaneous injection; fondaparinux (5-10 mg subcutaneous daily); warfarin with a target international normalized ratio (INR) of 2.0 to 3.0; vena caval filter; catheter-directed thrombolysis; and mechanical thrombectomy either percutaneous or open.

Presentation of data and statistical analysis. All reported values are mean ± SEM. Data were analyzed using frequency distribution. Data were compared using Student *t* test. A probability value of less than .05 was considered statistically significant.

RESULTS

Demographics. Females (61.7%) outnumbered males (38.3%) in the entire study population. No significant difference ($P = .90$) in gender was identified between the random sample (female, 61.9%; male, 38.1%) and the whole study population. Median age was 56.0 years [range, 4-97 years; 1.1% less than 16 years] (Fig 1, *A*). No significant difference ($P = .23$) in age was identified between the random sample (56.4 ± 0.5 years) and the whole study population (55.7 ± 0.3). The number of ultrasonographic studies did fluctuate from 1 year to another (Fig 2, *B*). Outpatient (74.3%) outnumbered inpatient (25.7%) studies. History of previous DVT (33.3%) and cancer (30.4%) were the most common risk factors in patients with DVT. Smoking (29.0%), recent surgery (27.5%), and hypercoagulability (5.8%) were also common risk factors in patients with acute DVT. Of the hypercoagulable patients, 54.5% demonstrated protein C deficiency and 18.2% hyperhomocysteinemia.

Prevalence of DVT. Acute DVT occurred in 6.8% and chronic DVT in 8.8% of patients studied. Iliofemoral DVT (iliac and/or common femoral vein) was identified in 49.3% of acute DVT and 36.0% of chronic DVT. No isolated iliac vein acute thrombus was identified (Fig 2). In

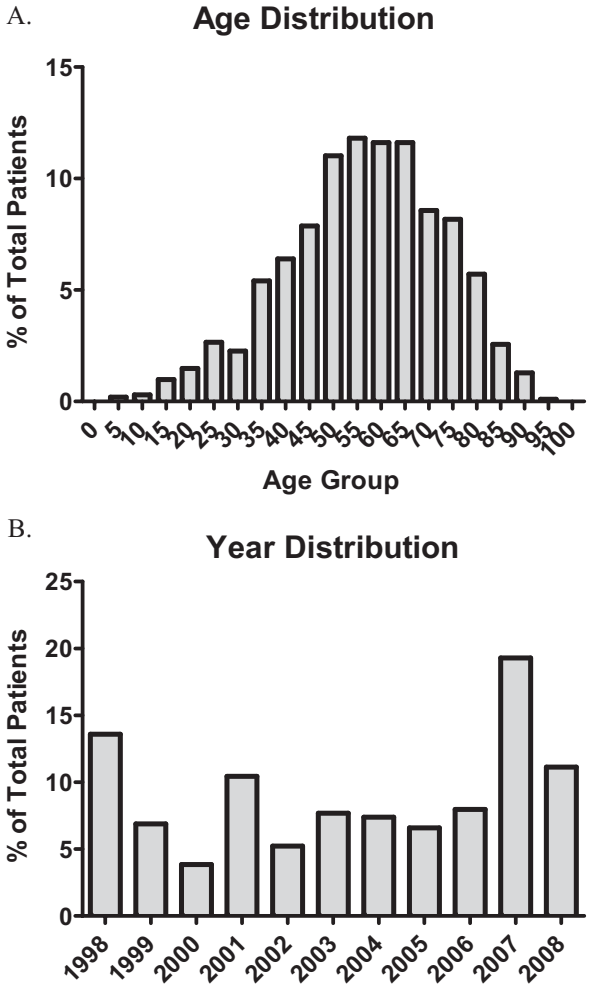

Fig 1. Demographic data. **A,** Age distribution of study population. **B,** Year distribution of study population.

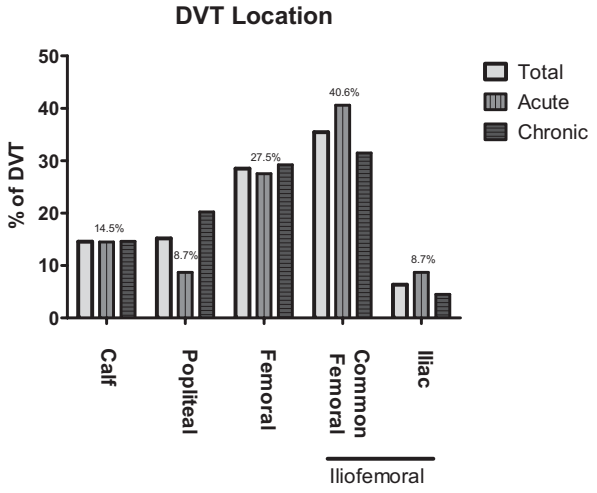

Fig 2. Deep venous thrombosis (*DVT*) prevalence stratified by location (most proximal extent of thrombus). Total, acute, and chronic DVT as labeled and in this sequence for each location.

2008, the referral base of our laboratory increased significantly, as the radiology department no longer provided venous duplex ultrasonography. Acute DVT occurred significantly less often during the 1-year period 2008 (5.3%) than the 10-year period 1998-2007 (7.6%) and may reflect practitioners who previously had used the radiology department for low probability screening exams now used the vascular lab. However, iliofemoral DVT as a component of acute DVT did not differ significantly. No change in system-wide DVT prophylaxis or treatment occurred during the conduct of this study.

Treatment of DVT. CDT was utilized in 60% and percutaneous mechanical thrombectomy in 20% of acute iliac DVT and was never used with common femoral, femoral, popliteal, or distal DVT (Fig 3). Overall, aggressive thrombus removal was utilized in 2.4% of DVT patients. Percutaneous mechanical thrombectomy was always used in conjunction with thrombolysis. Warfarin anticoagulation + full-dose unfractionated heparin or low-molecular-weight heparin bridging was the most common treatment for acute DVT (Fig 3). Surprisingly, full anticoagulation was not used in all popliteal DVT but was often used for distal DVT (Fig 3).

DISCUSSION

The results of this study demonstrate that in our large population of patients referred to the vascular lab for venous duplex study that: (1) iliofemoral DVT may be more prevalent than previously reported and represents a significant portion of acute DVT; and (2) current recommendations of acute thrombus removal for the treatment of iliofemoral DVT and high proximal DVT is underutilized.

Definitions of lower extremity DVT location may be confusing and are inadequate. Traditionally, lower extremity DVT is divided into *distal* (calf) or *proximal* (knee and higher) DVT.[14] Iliofemoral DVT is a subset of proximal DVT, but the exact definition of iliofemoral DVT varies. Some have defined that iliofemoral DVT must include a component of iliac vein thrombus (iliac vein DVT alone, iliac vein + common femoral DVT, and iliac vein + femoral DVT).[15] Common femoral DVT, which does not include iliac vein thrombus, is often classified not as iliofemoral DVT but as femoropopliteal DVT. In contrast, the Society of Interventional Radiology defines acute iliofemoral DVT as complete or partial thrombosis of any part of the *iliac vein and/or the common femoral vein* with or without associated femoropopliteal DVT, in which symptoms have been present for 14 days or less or for which imaging studies indicate that venous thrombosis has occurred within the past 14 days.[16] The common femoral vein segment is also included with iliac vein in the Society of Interventional Radiology (SIR) definition of iliofemoral DVT as both are the final pathway out of the leg and are crucial for the venous drainage of the lower limb. We concur with the definition of iliofemoral DVT as defined by the SIR and

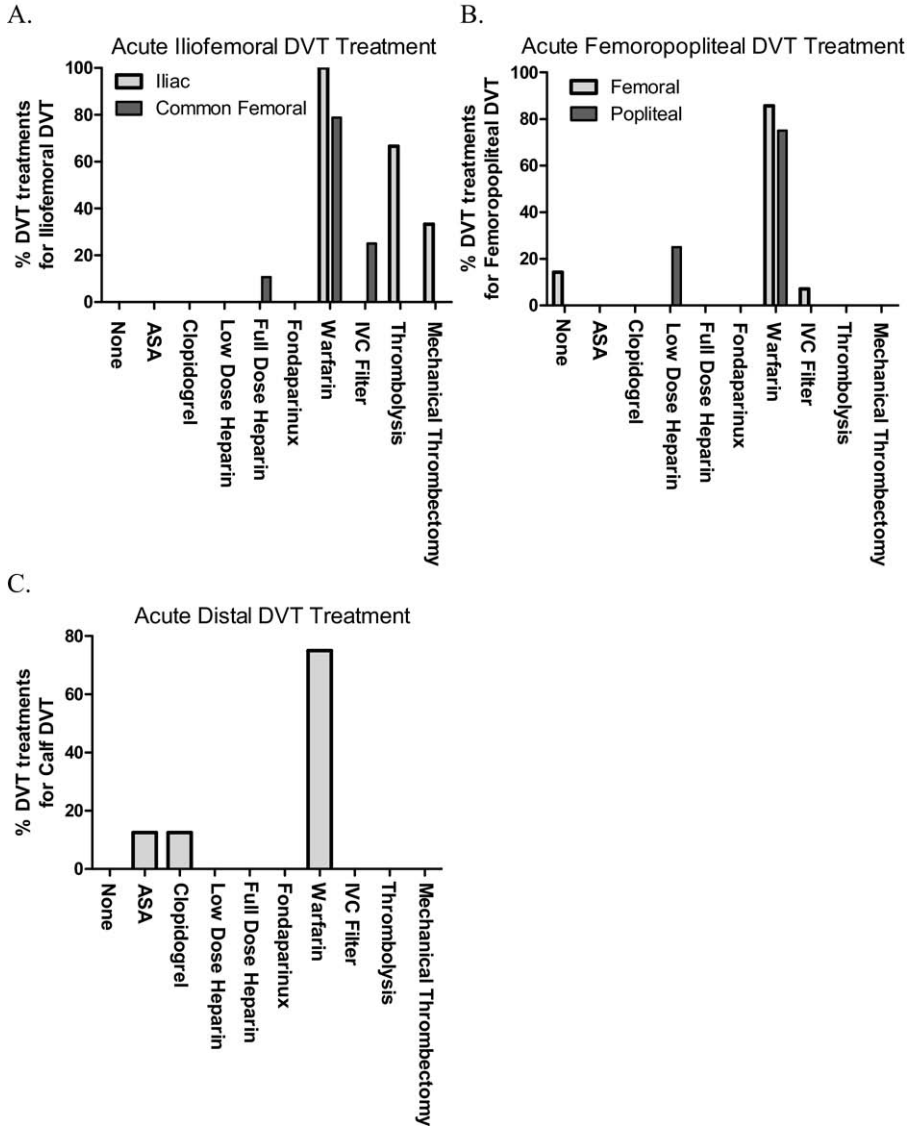

Fig 3. Acute deep venous thrombosis (*DVT*) treatment stratified by location (most proximal extent of thrombus). **A,** Iliofemoral DVT. **B,** Femoropopliteal DVT. **C,** Distal DVT. In all cases of warfarin treatment, therapeutic unfractionated heparin or low-molecular-weight heparin overlap bridging was also utilized.

herein refer to iliofemoral DVT as thrombus whose highest extent includes iliac vein or common femoral vein.

Few studies have addressed the prevalence of iliofemoral DVT. An older study of 189 patients with symptomatic DVT prior to widespread awareness of DVT prophylaxis and duplex ultrasonography utilized venography and determined that 43% of DVT involved the iliofemoral veins and 80% of DVT involved the high proximal venous system (femoral, common femoral, or iliofemoral veins).[17] In a more recent study investigating only acute proximal (non-calf DVT), Douketis et al found that iliac vein thrombosis occurred in only 4.4% of 1149 consecutive patients with symptomatic proximal DVT compared with 39.4% with popliteal vein thrombosis and 56.1% with femoral vein thrombosis.[1] In our study, which included proximal and distal DVT, we determined that acute iliac vein DVT comprised 8.7% of acute DVT and 4.5% of chronic DVT. Common femoral DVT (40.6%) and femoral DVT (27.5%) constituted the large majority of acute DVT in our study, which paralleled the prevalence of femoral vein thrombosis (56.1%) in the study by Douketis et al[1] Interestingly, our study population that developed acute DVT also demonstrated a high prevalence of prior DVT (33.3%); it remains plausible that prior DVT might predispose one to increased likelihood of developing iliofemoral DVT but this is unproven. Thus, iliac vein DVT may be more prevalent than previously realized, but certainly common femoral DVT (a subset of iliofemoral DVT) represents a significant burden of acute DVT.

Patients with iliofemoral DVT are at highest risk for postthrombotic morbidity including the postthrombotic syndrome (PTS).[1-3] Interestingly, recent studies also suggest that patients with extensive proximal (common femoral, femoral, or iliac vein) DVT have significantly worse PTS signs and symptoms than those with calf or popliteal vein DVT.[4-7] Stain et al determined that proximal DVT was the strongest risk factor of PTS with an odds ratio (OR) of 2.1 in a study of 406 patients with acute DVT.[5] Similarly, Kahn et al found that in a study of 387 outpatients with acute DVT, venous thrombosis of the common femoral or iliac vein were predictors of higher PTS severity over time (OR, 2.23 vs distal DVT).[6] The Multiple Environmental and Genetic Assessment (MEGA) study, a large population-based case control study of more than 2000 patients with venous thromboembolism, also revealed that DVT in the femoral and iliac vein was associated with a 1.3-fold increased relative risk (RR, 1.3; 95% confidence interval [CI], 1.1-1.6) of PTS compared with popliteal vein thrombosis.[7] Although many recent studies have focused on PTS after iliofemoral DVT, proximal DVT is greater in prevalence and may have a similar increased risk for PTS and reduced quality of life.

Because PTS occurs in 40% of patients after DVT despite adequate anticoagulation, numerous studies have focused on early thrombus removal and demonstrated that thrombolysis in addition to anticoagulation improves morbidity after acute proximal DVT.[8] Thus, the most recent American College of Chest Physicians (ACCP) 2008 guidelines recommends CDT in patients with extensive acute proximal DVT (eg, iliofemoral DVT), symptoms <14 days, and a low risk of bleeding.[9] Interestingly, the ACCP did not precisely define iliofemoral DVT nor did they define extensive acute proximal DVT. Nevertheless, despite rather impressive data in support for thrombus removal in extensive proximal DVT aimed at decreasing the PTS, clinicians are still reluctant to pursue thrombolytic therapy. The perceived risk of bleeding, renal failure, and even death with the use of thrombolytics in addition to the efficacy of standard anticoagulation in preventing PE and recurrent DVT remain barriers to early thrombolytic intervention. Indeed, in our population, thrombolysis was used in only 60% of iliac DVT and was never used in isolated infrainguinal DVT (common femoral and more distal disease).

Based on the manner in which we categorized our patients with DVT, the prevalence of calf vein thrombosis is also noted. There is significant controversy on the proper treatment of this disease state. The most recent ACCP clinical guidelines have suggested early therapeutic anticoagulation, which interestingly was applied in a significant number of our patients. The disappointing observation was that not all popliteal DVT were treated with therapeutic anticoagulation. It is unclear if this was due to a misunderstanding of the location of DVT or other factors.

Weaknesses of this study should be mentioned. Although this is a retrospective study, the pertinent laboratory did have a standardization protocol for study performance that aids in minimizing variability according to ICAVL standards. However, there is no ICAVL standard for iliac vein evaluation that leaved this a less well-defined area of study. In addition, ultrasound diagnosis of the iliac vein segment may have poor sensitivity, as decreased femoral phasicity may not occur with segmental iliac occlusion when full imaging is not possible. Body habitus further decreases ultrasonographic sensitivity of the iliac vein segments. Ultrasound findings were infrequently confirmed by other methodologies. The study population represented a subpopulation of our tertiary care population who were referred to the vascular lab for venous study, which may limit generalization to asymptomatic patients or other tertiary facilities whose referral patterns do not include a vascular ultrasound lab. Finally, the data analysis was limited by sampling design.

Further study is clearly needed to identify the prevalence and ideal treatment of iliofemoral DVT. In 2002, Elsharawy et al reported on one of the first randomized prospective trials of iliofemoral DVT patients treated with CDT + anticoagulation or anticoagulation alone that CDT improved venous patency and decreased venous reflux.[18] Similarly, early 6-month results from the Catheter-directed Venous Thrombolysis in acute iliofemoral vein thrombosis (CaVenT) study demonstrate increased iliofemoral patency (36% vs 64%) and decreased venous obstruction (49.1% vs 20.0%) in the CDT arm.[19] The Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial is an ongoing prospective trial of iliofemoral versus femoropopliteal DVT patients randomized to medical management with standard anticoagulation versus catheter-directed thrombolysis with a primary outcome of postthrombotic syndrome over a 24-month follow-up.[20] We suspect that further prospective randomized trials such as these may suggest greater efficacy of early clot removal in iliofemoral DVT.

AUTHOR CONTRIBUTIONS

Conception and design: PC, MD, JC, BF, JK, DJ
Analysis and interpretation: PC, MD
Data collection: PC, JK, DJ
Writing the article: PC, MD
Critical revision of the article: PC, MD, JC, BF
Final approval of the article: PC, MD
Statistical analysis: PC
Obtained funding: PC, MD
Overall responsibility: PC

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Submitted Mar 7, 2010; accepted May 27, 2010.